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The risk of cervical adenocarcinoma in patients infected with human papillomavirus type-18 is three times higher than other high-risk types



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ABSTRACT

Introduction: cancer is still a health problem worldwide. Cervical cancer is the second most common cancer in women in developing countries. High-risk Human Papillomavirus (HPV) is well recognized as the causative agent of cervical cancer. Squamous cell carcinoma and adenocarcinoma are the most and the second most common histopathological type. HPV genotypes probably correlate to histopathological type. This study aims to prove that infection by HPV-18 gives a greater risk for the occurrence of cervical adenocarcinoma compared with infection by other high-risk HPV types.

Methods: This study was case control study that used adenocarcinoma with HPV-18 positive patients as the case group and adenocarcinoma with positive with other high-risk HPV types as the control group.

Histopathological diagnosis performed on H & E stain. Genotyping of HPV used SPF-10 and specific E7-primer by LiPA. Bivariate analysis was employed to calculate odds ratios (ORs) and Pearson's χ^2 test was applied.

Result: Total number of adenocarcinoma observed in this study were 42 patients, consisted of 12 cases and 30 controls. The most prevalence adenocarcinoma occurred in the age group 41-50 years. The risk of adenocarcinoma in patients with HPV-18 infection was 2.88 fold compared with infection by other high-risk HPV types (95% CI = 1.12-7.38; $p = 0.024$).

Conclusion: HPV-18 infection caused cervical adenocarcinoma is 3.0 more than other high-risk HPV types

Keywords: cervical adenocarcinoma, HPV-18, histopathological type

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INTRODUCTION

Cervical cancer accounts for nearly 12% of all female cancers and is the second most common type of malignancy in women worldwide.^{1,2} Each year approximately 510,000 new cases are reported, and nearly 80% occur in developing countries.³ Cervical cancer is the fourth leading cause of cancer death in females worldwide. It accounts for 9% mortality (529,800) of the total new cancer cases and 8% (275,100) of the total cancer deaths among females.⁴

Longstanding infections with high-risk Human papillomavirus (HPV) has been identified as a key factor or etiological agents in the development of cervical cancer.⁴⁻⁸ More than 100 HPV genotypes are known at the genetic level¹ and more than 50 HPV genotypes infect the female genital tract.³ HPV genotypes are classified according to their association with cervical cancer and precursor lesions into high-risk or oncogenic HPV and low-risk HPV genotypes.³ Among these HPV genotypes, 15 HPV types have been classified as high-risk types that associated with varying degrees with cervical cancer, and three types have been classified as a probable high risk.^{1,9} The most prevalent high-risk HPV genotypes which infect uterine cervix worldwide,

are 53% HPV-16, followed by 15% HPV-18, 9% HPV-45, 6% HPV-31 and 3% HPV-33.³ In the cases of cervical cancer, HPV-16 and HPV-18 are responsible for the largest percentage i.e. more than 90%.^{2,6,10,11} Different high-risk HPV genotypes seem to confer different degrees of risk for cervical cancer and its precursor lesions.⁹ As a consequence, many studies assess the additive value of HPV genotyping in cervical screening.¹⁰

Numerous prognostic factors influence cervical cancer including clinical staging, lymph nodes metastasis, parametrial involvement and invasion of the lymphovascular space. The previous study found that the presence of HPV-18 also considered an independent prognostic factor for a poor outcome in early stage cervical cancers.² Among histologic types of cervical cancer, squamous cell carcinoma (SCC) and adenocarcinoma are the first and the second most common type.^{6,12} Incidence rates of cervical adenocarcinoma, which accounts for 10–20 % of all cervical cancers, have increased continuously in developed countries during the last two decades, as opposed to those of squamous cell carcinoma, due to the introduction of the Pap smear.^{4,8} As the vast majority of both SCC and

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Table 1 The Age Range of Cervical Carcinoma Patients Infected with HPV-18

| Age range (years) | Number | Percentage (%) |
|-------------------|--------|----------------|
| 21-30 | 1 | 44.55 |
| 31-40 | 2 | 9.09 |
| 41-50 | 11 | 50.00 |
| 51-60 | 4 | 18.18 |
| 61-70 | 4 | 18.18 |
| Total | 22 | 100.00 |

Table 2 Cervical Carcinoma Patient Infected by High Risk HPV According to Histopathological Type

| Histopathological Type | Number | Percentage (%) |
|-------------------------|--------|----------------|
| Adenocarcinoma | 42 | 33.87 |
| Squamous Cell Carcinoma | 81 | 65.32 |
| Adenosquamous Carcinoma | 1 | 0.81 |
| Total | 124 | 100.00 |

Table 3 The Risk of Cervical Adenocarcinoma in Patient Infected with HPV-18

| | Adenocarcinoma | | OR | CI | p |
|-----------------|----------------|----------|------|-----------|-------|
| | Positive | Negative | | | |
| HPV-18 Positive | 12 | 10 | 2.88 | 1.12-7.38 | 0.024 |
| HPV-18 Negative | 30 | 72 | | | |

adenocarcinoma caused by HPV-16 and HPV-18, women with detected HPV-16 and HPV-18 infections should be offered more intensive follow-up schemes compared to women infected with other high-risk HPV types.⁹

HPV genotypes probably correlate to histopathological type. Many previous studies found that infection by HPV-18 is more prevalent in adenocarcinoma (37%) and its precursor than SCC (12%).^{5,7,13} Study by Dahltrom et al. (2010) found an HPV-18 positive smear was associated with increased risks for adenocarcinoma in situ and invasive adenocarcinoma, compared to an HPV-18 negative smear.⁸ Most HPV-18 infections are asymptomatic and are cleared by the immune system. Factors that favor HPV-18 infection are progress to cervical cancer are poorly understood, may be implicated a role for HPV-18 genetic variation.⁷ Screening for these HPV types is a useful tool for improving the prevention and/or early detection of cervical adenocarcinomas.⁸ These important prognostic factors for each histological type may be beneficial and necessary for optimal selection of treatment modality, monitoring treatment response, and

planning of follow-up.¹⁴ This study aimed to prove that infection by HPV-18 gives a greater risk for the occurrence of cervical adenocarcinoma compared with infection by other high-risk HPV types.

RESEARCH DESIGN AND METHODS

Specimen collection

This study design was case control study that was conducted during the years 2013-2014. The materials of this study were the paraffin-embedded tissue, which had been diagnosed as cervical adenocarcinoma at Laboratory of Anatomical Pathology Faculty of Medicine Udayana University/ Sanglah General Hospital. The adenocarcinoma sample with HPV-18 positive as the case group and adenocarcinoma positive with other high-risk HPV types as the control group.

HPV DNA Detection and Genotyping

For detection and genotyping of HPV DNA, the paraffin-embedded tissues from cervical biopsy diagnosed as adenocarcinoma were sent to Department of Pathology Leiden University Medical Centre (LUMC) Netherland, and Molecular Biology Laboratory Unit, Faculty of Medicine Udayana University. SPF10 primers at several dilutions were used to amplify the DNA. The positive product then performed using specific probes type-specific E7 primer by LiPA to know the evidence of HPV-18 and another HPV type. A total of 124 cervical cancer patients were included in this study.

Statistical Analysis

The descriptive characteristics of the data subject were tabulated, and statistical analysis was performed using Pearson's X² Test with P-value less than 0.05 was considered significant. In order to calculate the odds ratios (ORs) for the risk of cervical adenocarcinoma associated with HPV-18, bivariate analysis was employed with 95% confidence interval (CIs).

RESULTS

The age range of cervical carcinoma patients infected with HPV-18, cervical carcinoma patient, infected by high-risk HPV according to histopathological type, and the risk of developing cervical adenocarcinoma associated with HPV-18, display in Table 1, 2 and 3 respectively.

A total of 124 cervical carcinoma patients infected by high-risk HPV were included in this study. Of these patients, the infection by HPV-18 was as many as 22 samples (17.74%) and by other

high-risk HPV as many as 102 (82.26%). The youngest patient infected by HPV-18 was 21 years old, and the oldest was 70 years old. The most prevalence occurred in the age group 41-50 years as many as 11 samples (50%).

Cervical carcinoma patients infected by high-risk HPV according to histopathological type in this study showed the squamous cell carcinoma was the most common, as many as 81 samples (65.32%), followed by 42 samples (33.87%) adenocarcinoma and 1 sample (0.81%) adenosquamous carcinoma.

Table 3 show cervical adenocarcinoma infected with HPV-18 were 12 samples, while cervical adenocarcinoma infected with other high-risk HPV type were 30 samples. The presence of HPV-18 infection was statistically significantly associated with an increase of 2.88-fold in the risk of adenocarcinoma compared with patients infected with other HPV types (95% CI = 1.12-7.38; $p = 0.024$).

DISCUSSION

This study found patients infected by HPV-18 was as many as 22 samples (17.74%) of all cervical carcinoma. Infection by another high-risk type, including type 16, was as many as 102 samples (82.26%). Some of the previous studies showed the prevalence of HPV infection in cervical cancer was 95% with marked increased risk of cervical cancer attributed to HPV-16 and HPV-18.^{2,3,4,9,15} Chrysagi et al. (2016) has also shown that HPV-16 and 18 were the most common (73.08%) and the second most common (35.90%) HPV in cervical cancer.⁴ Another study found more than 90% cervical cancers are infected with HPV-16, 18, 31 and 45, and half of these cases are infected with HPV-16.¹⁶ In Jakarta the two most common HPV types are HPV-16 (35%) and HPV-18 (28%).¹⁷ A study in three regions in Indonesia, namely Jakarta, Tasikmalaya and Bali found the four most common types are HPV-52 (23.2%), HPV-16 (18%), HPV-18 (16.1%) and HPV-39 (11.8%). In Bali the three most common types are HPV-52 (18%), HPV-16 (15%) and HPV-18 (12%).¹⁸ The results of this study indicate the prevalence of patients infected with HPV-18 slightly higher than previous studies.

The age range of sample with cervical carcinoma infected with HPV-18 in this study was 21-70 years. The most prevalence occurred in the age group 41-50 years as many as 11 samples (50%). The youngest was 21 years old and the oldest 70 years old. Another research found that infection by HPV-18 was more common in patients with younger age namely by 46%, compared to the old age that was equal to 26%.⁶ Study by Bruni et al. found age-specific HPV distribution presented with

the first peak at younger ages (<25 years) which is in accordance with the result of this study.¹⁹

A total of 124 cervical carcinoma patients were included in this study. Of these patients, distribution of HPV infected cervical carcinoma according to histopathological type showed the squamous cell carcinoma was the most common, as many as 81 samples (65.32%), followed by 42 samples (33.87%) adenocarcinoma and 1 sample (0.81%) adenosquamous carcinoma. The results of this study was in accordance with the results of the previous studies that found that approximately 90% of cervical cancers are squamous cell carcinoma derived from squamous metaplasia in the transformation zone while the remaining 10% is adenocarcinoma derived from endocervical columnar epithelial.¹²

In this study, the infection by HPV-18 provide 2.88 times greater risk for the occurrence of cervical adenocarcinoma (OR = 2.88; 95% CI = 1.12-7.38; $p = 0.024$). The previous study also got the same result that the prevalence of HPV-18 infection in adenocarcinoma (39%) which is greater than that of squamous cell carcinoma (18%) and statistically significant ($p < 0.001$).⁶ The study by Chen et al. also showed a significant result that is 37.0% for HPV-18 infection in cervical adenocarcinoma and 12% of squamous cell carcinomas (SCC).⁷ The prevalence of HPV-18 infection is greater in adenocarcinoma and its precursor lesions.^{5,13} HPV-18 is the most common type of infection in adenocarcinoma (55%), followed by HPV-16 (32%) and HPV-45 (10%).¹⁶ The study by Bulk et al. found that infection by HPV-18 posed the greatest risk compared with other types HPV for the occurrence of cervical adenocarcinoma. Cervical adenocarcinoma is significantly more frequently associated with HPV18 (OR_{MH} = 15.0; 95% CI = 8.6-26.1).⁵ The HPV-18 positive smear was associated with increased risks for adenocarcinoma in situ and invasive adenocarcinoma.⁸ The greatest risk for the occurrence of adenocarcinoma is associated with HPV-18 infection.⁶

CONCLUSION

In conclusion, it appears that HPV-18 could increase the risk of cervical adenocarcinoma almost three times greater than the other HPV types and tend to occur more often at the younger age.

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